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ELI LILLY AND COMPANY

By R. Craig Tucker Date October 6, 2008

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

First Appellant:	BLANCO-PILLADO, Maria-Jesus	Group Art Unit:
Serial No.:	10/552131	1625
Filed:	April 14, 2004	Examiner:
		Chang, Celia C

PCT Nat'l Entry
Date (if applicable): October 11, 2005

For: (PIPERIDINYLOXY)PHENYL, (PIPERIDINYLOXY)PYRIDINYL, (PIPERIDINYLSULFANYL)PHENYL AND (PIPERIDINYLSULFANYL)PYRIDINYL COMPOUNDS AS 5-HT1F AGONISTS

Docket No.: X14441

BRIEF FOR APPLICANTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants appeal from the final rejection dated February 14, 2008, of claims 1, 9, 14-15, and 29-32 of this application. Appellants' Brief in compliance with 37 C.F.R. 41.37 is as follows.

10/08/2008 HVUONG1 00000029 050840 10552131

01 FC:1402 540.00 DA
02 FC:1252 490.00 DA

Real Party in Interest

The real party in interest is Eli Lilly and Company, the owner of all interests in the invention in their entirety by virtue of assignment from all inventors, as recorded with the USPTO, on July 14, 2006, REEL/FRAME: 017933/0713w, comprising 10 pages.

Related Appeals and Interferences

There are no related appeals, interferences, or judicial proceedings known.

Status of Claims

Claims 1, 9, 14, 15, and 29-32 are pending in the application.

Claims 2-8, 10-13, and 16-28 have been canceled.

All pending Claims, Claims 1, 9, 14, 15, and 29-32, stand finally rejected.

The rejections of all pending Claims, Claims 1, 9, 14, 15, and 29-32 are being appealed.

Status of Amendments

No amendments have been filed subsequent to the final rejection. The Claims stand as amended in Applicant's last response and are as considered for the final rejection.

[Note: Examiner may erroneously consider Applicant's amendments to the Claims, submitted with Applicant's response of November 28, 2007, to have not been entered, due to erroneous treatment of said amendments after considering said amendments to be new matter; the Final Rejection is not entirely clear on this point. The Examiner "removed" the alleged new matter for all remaining consideration of the application in Examiner's Final Rejection of February 14, 2008, in contradiction to M.P.E.P. 706.03(o), examiner's note 3, which states, "As to any other appropriate prior art of 35 U.S.C. 112 rejection, the new matter must be considered as part of the claimed subject matter and cannot be ignore." Thus Applicants consider the amendments to have been entered and the Claims to currently stand as so amended.]

Summary of Invention

In general, the present invention is drawn to a family of compounds discovered to be potent and selective 5-HT_{1F} agonists, to pharmaceutical compositions containing said compounds, and to methods of treatment or prevention of migraine using said compounds.

Specifically, independent Claim 1 as amended is drawn to compounds of formula I, as found on page 3, line 16 through page 4, line 15, of the specification as filed, as limited by preferred embodiment 42), found at page 14, lines 12-15, of the Specification as filed.

Independent Claim 9 is drawn to pharmaceutical compositions comprising the compounds according to Claim 1, as described in the Specification at page 4, lines 16-18, and page 170, line 24 through page 173, line19.

Independent Claim 14 is drawn to a method of treatment or prevention of migraine using the compounds of the invention as limited in Claim 1, as described in the Specification at page 5, lines 5-8, and page 163, line 3, through 167, line 25.

Independent Claim 29 is drawn to compounds of formula I, as found on page 3, line 16 through page 4, line 15, of the specification as filed, as limited by preferred embodiment 10) (page 12, lines 31-32) combined with preferred embodiment 40) (page 14, lines 8-9), said combination as described for further preferred embodiments at page 14 lines 24-27 of the Specification as filed.

Independent Claim 30 is drawn to pharmaceutical compositions comprising the compounds according to Claim 29, as described in the Specification at page 4, lines 16-18, and page 170, line 24 through page 173, line19.

Independent Claim 31 is drawn to a method of treatment or prevention of migraine using the compounds of the invention as limited in Claim 29, as described in the Specification at page 5, lines 5-8, and page 163, line 3, through 167, line 25.

Grounds of rejection to be reviewed on appeal

1. Whether Applicants' amendments to Claim 1, 9, 14 and 15 of Nov. 28, 2007, introduced new matter and were therefore properly rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

2. Whether, Applicants' new Claims 29 through 32 introduced new matter and were therefore properly rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

3. Whether Claims 1, 9, 14, 15, and 29-32 are unpatentable under 35 U.S.C. 102(a), (b), or (e) in view of Pruecher, Gaster, Eriksson, Chen, or Askew.

4. Whether Claims 1, 9, 14, and 15 are unpatentable under 35 U.S.C. 112, first paragraph as being based on a non-enabling disclosure vis a vis data and/or guidelines for the compounds crossing the blood brain barrier and/or using the compounds in the methods of treatment/prevention of migraine.

5. Whether Claims 14 and 15 are unpatentable under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement and enablement requirement vis a vis describing/enabling the prevention of migraine.

6. Whether Claims 29-32 are unpatentable under 35 U.S.C. 112, first paragraph as being based on a non-enabling disclosure vis a vis data and/or guidelines for the compounds crossing the blood brain barrier and/or using the compounds in the methods of treatment/prevention of migraine.

7. Whether Claims 31 and 32 are unpatentable under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement and enablement requirement vis a vis describing/enabling the prevention of migraine.

8. Whether Claims 9 and 30 are unpatentable under 35 U.S.C. 112, first paragraph as being indefinite for failing to include quantitative limitations.

[Applicants note that no mention was made in the Final Rejection of the non-final rejection of 6/28/2007, of original Claims 1-7, 9, and 14 on non-statutory obviousness-type double patenting over co-pending application No. 10/569,109 in

view of King. In that this rejection was rebutted in Applicant's response of 11/28/2007, and that it is a requirement that all grounds of rejection in a Final Rejection must be recited in detail, Applicants therefore presume this ground of rejection has been withdrawn.]

Arguments

1. Whether Applicants' amendments to Claim 1, 9, 14 and 15 of Nov. 28, 2007, introduced new matter and were therefore properly rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

Examiner's determination of Applicants' amendments to Claims 1 and 14, carried by reference into Claims 9 and 15, introduce new matter is based on an incomplete and erroneous reading of the plain meaning of the claim. Examiner acknowledges that the limitations of R^{1-5} were proper as having basis in the Specification, presumably as being preferred embodiment 42) as detailed in Applicants' Remarks to the Amendments. The Examiner then asserts that the Specification does not support the further limitation, specifically the limitation of R^6 to be hydrogen. (See Final Rejection, Detailed Action, point 2.)

The simple reading of the unamended definition of R^6 clearly states that "R^6 is hydrogen or C_1-C_3 alkyl optionally substituted with one to three fluoro substituents, provided that R^6 may be C_1-C_3 alkyl only when R^5 is other than hydrogen;" (Emphasis added)(See Specification page 4, lines11-12, and original Claims 1, 10, 12, 14, and the Abstract.) Thus, when R^5 is limited to hydrogen, R^6 may not be anything but hydrogen as well; it is the only other option beside C_1-C_3 alkyl in the Markush. In that the general formula has a substituent R^6, said substituent must be defined and the only definition allowable when R^5 is limited to hydrogen, is that R^6 must also be hydrogen.

Thus, the Examiner's rejection of Claims 1, 9, 14, and 15, on new matter is clearly erroneous and must be withdrawn.

2. Whether, Applicants' new Claims 29 through 32 introduced new matter and were therefore properly rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

Examiner's determination that Applicants' new Claims 29-32 introduce new matter is based on an incomplete, over-restrictive, and erroneous reading of the plain meaning of the Specification's description of the preferred embodiments. Examiner

acknowledges that the page 12 of the Specification recites a preferred selection of R^1 as limited in Claim 29. as detailed in Applicants' Remarks to the Amendments. The Examiner asserts that the Specification does not provide basis for the combination of this selection with the other recited limitations for other substituents, ignoring Applicants Remarks in their response regarding the basis for the selection of substituents for the new Claims. (See Final Rejection, Detailed Action, point 2.)

Applicants Point out that the Specification specifically provides for preferred selections of each substituent, R^{1-6}, as well as certain sets of preferred substituents. Among these are preferred embodiment 10), limiting R^1 to "substituted or unsubstituted . . . pyridinyl and thiophenyl", and preferred combination for R^{2-5} 40), "R^2 is hydrogen or methyl, and R^3, R^{4a}, R^{4b}, R^{4c} if present, and R^5 are each hydrogen". Then, as is only reasonable, the Specification provides that further preferred embodiments are compounds that combine these preferred selections for each of the various substituents. Specifically, page 14, lines 24-26 of the Specification reads, "It will be understood that the above classes may be combined to form additional preferred classes, as for example the combination of preferred selections for two or more substituents." The Specification goes on to provide certain exemplary combinations.

It is admitted that due to typographical errors in numbering, the intended delineation of preferred R^1's being combined with the preferred selections for the other substituents was not properly completed. For example, preferred embodiment 46) was intended to combine the preferred selections for R^1 with preferred embodiment 28, which limits R^5 to hydrogen, rather than preferred R^1 embodiments 10-15 only with a different, broader selection for R^1. More particularly for new Claims 29-32, preferred embodiment 63) was intended to combine any one of the preferred selections for R^1, (1-15), with preferred embodiment 28) (R^5 is hydrogen)(this was meant to be combination 46)), with preferred embodiment 17) (R^2 is hydrogen or methyl)(this is preferred combination 49), with preferred embodiment 21) (R^3 is hydrogen)(this is preferred combination 61), with preferred embodiment 24)($R^{4a,4b,4c}$ each hydrogen). This combination 63 is equivalent to the combination of preferred R^1 embodiment 10) with preferred combination for R^{2-5} embodiment 40.

Although the description's numbering errors failed, the specific description that preferred embodiments are the combinations of the preferred selections for each

substituent found on page 14, lines 24-26 does not, such that the basis for new claim 29's combination of embodiment 10) with 40), is enabled and described. This scope is likewise supported by the bulk of the exemplified compounds having non-phenyl R^1 substituents.

As such, Applicants new Claims 29-32 in fact do not constituent new matter and the Examiner's rejection on this ground must be withdrawn.

3. Whether Claims 1, 9, 14, 15, and 29-32 are unpatentable under 35 U.S.C. 102(a), (b), or (e) in view of Pruecher, Gaster, Eriksson, Chen, or Askew.

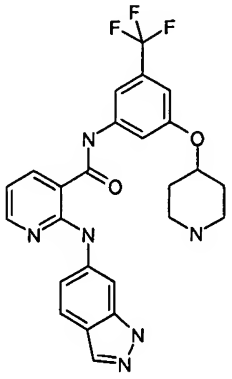
Examiner improperly removed Applicants' Claim amendments after asserting her new matter rejections in contravention of the rules to the contrary. Based on this erroneous action, the rejections based on 102 were maintained. M.P.E.P. 706.03(o), examiner's note 3, which states regarding amendments to the claims considered rejected under 35 U.S.C. 112 for new matter, "As to any other appropriate prior art of 35 U.S.C. 112 rejection, the new matter must be considered as part of the claimed subject matter and cannot be ignore."

This clearly was not done. The Examiner was required to consider the 102 and 112 rejections of record as applied to claims as amended. Considering the Claims as amended, the 102 analysis proceeds follows:

Originally presented Claims 1-4 were rejected in the first office action under 35 U.S.C. 102(b) in view of Pruecher, Gaster and Eriksson. Each of these references describe similar compounds wherein R^1 is methyl. The present amended claims require R^1 to be substituted phenyl (Claims 1, 9, 14 &15) or unsubstituted or substituted pyridinyl or thiophenyl (Claims 29-32). Thus the Pruecher, Gaster and Eriksson references clearly do not anticipate the presently presented Claims and the rejection must be withdrawn.

Originally presented Claims 1-5 and 9 were rejected under 35 U.S.C. 102(a), (b), or (e) in view of Chen or Askew. Chen discloses kinase inhibitors for the treatment of various cancers. The compounds disclosed in the Chen reference all

have a common core of a heterocyclic moiety having an amino-linked heterocycle substituent (either bicyclic or monocyclic with a second cyclic moiety directly bonded to the first) and a second amide linked substituent. In this reference, it is permitted and once exemplified (1 of 475 exemplified compounds) that this amide linked moiety be a pyridinyloxyphenyl moiety as cited in the Office Action (RN 454481-41-5 is example 74 in the reference):

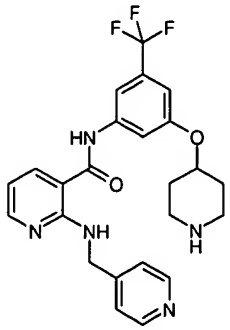


In this reference example, the pyridyl moiety roughly corresponds to R^1 of the presently claimed compounds, wherein R^1 is substituted heterocycle, which would here be substituted pyridyl. It is noted that the amine-linked heterocyclic moiety in all of the reference compounds, in this example, indazol-6-yl-amino, form an integral part of the compounds disclosed in the reference.

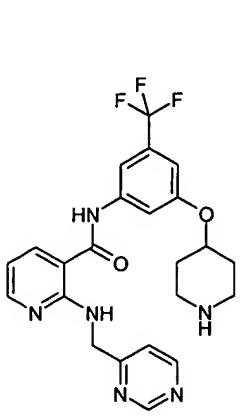
However, it is noted that the presently claimed compounds do not allow such substitutions on the R^1 moiety (see page 8, lines 13 through page 9, line 15). Specifically, R^1 substituents according to the present description may not be amine linked substituents and may not be bicyclic moieties, let alone bicyclic heteroaryls as described in the Chen reference. Therefore, the Chen reference can not be said to anticipate the compounds of the present invention. Thus the rejection must be withdrawn.

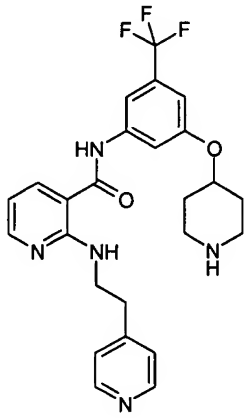
The Askew reference is related to the Chen reference (assigned to Amgen, shares 11 of 21 inventors, is drawn to compounds of a similar structure for treatment of the same indications and shares the same priority filing dates) and similarly discloses kinase inhibitors for the treatment of various cancers. As in the Chen reference, a large substituent off the core structure of the Askew compounds may be

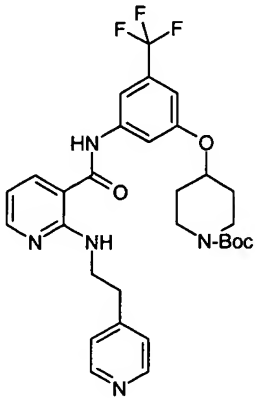
selected to be an amide linked pyridinyloxyphenyl moiety, and such is exemplified in example 533, RN 453561-92-7, as cited in the Office Action:



Three other compounds of the 1194 examples in the Askew reference have amide linked pyridinyloxyphenyl moieties: Examples 543, 838, and 839, respectively:







As with the analysis in regard to the Chen reference, it is noted that the presently claimed compounds do not allow amine linked substituents on R^1 as described in the Askew reference, which amine-linked heterocycles form an integral part of all the reference compounds. Therefore, the Askew reference can not be said to anticipate the compounds of the present invention. Thus the rejection must be withdrawn.

It is clear that when the amendments to the Claims are properly considered, none of the cited references anticipate the claimed scope. All 35 U.S.C. 102 rejections were clearly obviated by Applicants' amendment and the rejections must be withdrawn.

4. Whether Claims 1, 9, 14, and 15 are unpatentable under 35 U.S.C. 112,

first paragraph as being based on a non-enabling disclosure vis a vis data and/or guidelines for the compounds crossing the blood brain barrier and/or using the compounds in the methods of treatment/prevention of migraine.

Originally presented Claims 1-7, 9, and 14-15 were rejected under 35 U.S.C. 112, first paragraph. As properly amended, these rejections would stand against present Claims 1, 9, 14, and 15. In the Examiner's estimation, Applicants' showing of compounds having potent agonist activity at the 5-HT_{1F} receptor coupled with evidence correlating such activity with a therapeutic benefit is insufficient to enable the presently claimed invention. Examiner places on Applicants the further arbitrary requirement that evidence be shown that the presently claimed compounds solve an additional technical problem, to wit, the crossing of the blood brain barrier, using statements in the Phebus reference as a basis for making such a requirement. Further the Examiner considers the Specification lacking in sufficient guidelines as to how to use the compounds to operate the method of treating/preventing migraine.

It is first noted that it has never been a requirement under U.S. patent law that clinical data be required to enable a pharmaceutical composition of matter claim or a pharmaceutical method of treatment claim. To comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). It is in fact long been held as sufficient to show an in vitro activity such as receptor binding affinity, combined with some reasonable nexus between that in vitro activity and the therapeutic benefit claimed. The Specification points out this correlation in the background and in the biological sections of the application, particularly by reference to the detailed correlation between 5-HT_{1F} receptor activity and migraine found in US Patent 5,708,008 (page 163, line 6). The present discovery is of novel, non-obvious 5-HT_{1F} receptor agonists, where it is known that agonism of the 5-HT_{1F} receptor may reasonably be expected to have therapeutic benefit in the treatment or prevention of migraine by virtue of this activity.

Further, it is respectfully submitted that the Examiner has overlooked or ignored the description of formulation and administration of compounds of the present invention for the claimed methods of treatment found in the Specification at page 170, line 15 through page 173, line 19. This description clearly informs one of ordinary skill in the art how to work the methods of treatment/prevention.

Lastly, though it is not necessary for a finding of enablement as discussed above, the Examiner seems to have also overlooked or ignored the protein extravasation assay described in the Specification at page 166, line 11 through page 167, line 25, which assay is an in vivo rat assay, which would not be effective if the test compounds did not effectively reach the target tissues. There is therefore no basis for a rejection based on description or enablement for the Claimed compounds or the Claimed methods of treatment utilizing the compounds. The rejection must be withdrawn.

5. Whether Claims 14 and 15 are unpatentable under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement and enablement requirement vis a vis describing/enabling the prevention of migraine.

Originally presented Claims 14-15 were rejected rejected under 35 U.S.C. 112, first paragraph. This rejection would presumeably be applied equally to present Claims 14 and 15. In the Examiner's estimation, a claim for the prevention of migraine requires showings of specific dosages different from those described in the Specification as noted above along with evidence of non-toxicity at such doses, as well as a 100% cure rate. The Examiner is referred to the above arguments as they pertain directly to this second rejection based on section 112. Examiner is also directed to M.P.E.P. 2164.01(c), 2nd paragraph

> "For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The

applicant need not demonstrate that the invention is completely safe. See also MPEP § 2107.01 and § 2107.03."

The asserted additional requirements for clinical data are simply not the law with regard to methods of treatment. Note that there is no claim limitation to the exact dose to be used or that such dose be free of any associated toxicities. (Again, "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). It is in fact well known in the art how to determine if a patient is a candidate for preventative treatment for migraine. The National Migraine Association website states:

> First, preventive, or prophylactic, medications are prescribed to prevent or reduce the number of attacks in patients who experience frequent Migraines, typically two or more per month. In general, these medications act over time to prevent blood-vessel swelling; however, they do not treat the Migraine-associated symptoms and are non-selective. Many sufferers using preventive treatments will still have to take attack-aborting medications to relieve pain and other symptoms.

Women's Health Channel states:

> Prophylactic Treatment: Preventative medication may be prescribed for patients who have frequent headaches (3 or more a month) that do not respond to abortive treatment. Studies have shown that as many as 40% of these patients may benefit from preventative treatment.

It is well within the skill of the art to take the guidance given as referenced above to set appropriate dosing for any given clinical candidate selected among the compounds within the scope of the claims and for a physician to adjust such dosing as needed for a given patient under their care. Furthermore, it has never been a requirement that a pharmaceutical agent provide a 100% cure rate to be patentable. The rejection must be withdrawn.

6. Whether Claims 29-32 are unpatentable under 35 U.S.C. 112, first paragraph as being based on a non-enabling disclosure vis a vis data and/or guidelines for the compounds crossing the blood brain barrier and/or using the compounds in the

methods of treatment/prevention of migraine.

Claims 29-32 stand rejected under 35 U.S.C. 112, first paragraph. In the Examiner's estimation, Applicants' showing of compounds having potent agonist activity at the 5-HT_{1F} receptor coupled with evidence correlating such activity with a therapeutic benefit is insufficient to enable the presently claimed invention. Examiner places on Applicants the further arbitrary requirement that evidence be shown that the presently claimed compounds solve an additional technical problem, to wit, the crossing of the blood brain barrier, using statements in the Phebus reference as a basis for making such a requirement. Further the Examiner considers the Specification lacking in sufficient guidelines as to how to use the compounds to operate the method of treating/preventing migraine.

It is first noted that it has never been a requirement under U.S. patent law that clinical data be required to enable a pharmaceutical composition of matter claim or a pharmaceutical method of treatment claim. To comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). It is in fact long been held as sufficient to show an in vitro activity such as receptor binding affinity, combined with some reasonable nexus between that in vitro activity and the therapeutic benefit claimed. The Specification points out this correlation in the background and in the biological sections of the application, particularly by reference to the detailed correlation between 5-HT_{1F} receptor activity and migraine found in US Patent 5,708,008 (page 163, line 6). The present discovery is of novel, non-obvious 5-HT_{1F} receptor agonists, where it is known that agonism of the 5-HT_{1F} receptor may reasonably be expected to have therapeutic benefit in the treatment or prevention of migraine by virtue of this activity.

Further, it is respectfully submitted that the Examiner has overlooked or ignored the description of formulation and administration of compounds of the present invention for the claimed methods of treatment found in the Specification at

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Lastly, though it is not necessary for a finding of enablement as discussed above, the Examiner seems to have also overlooked or ignored the protein extravasation assay described in the Specification at page 166, line 11 through page 167, line 25, which assay is an in vivo rat assay, which would not be effective if the test compounds did not effectively reach the target tissues. There is therefore no basis for a rejection based on description or enablement for the Claimed compounds or the Claimed methods of treatment utilizing the compounds. The rejection must be withdrawn.

7. Whether Claims 31 and 32 are unpatentable under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement and enablement requirement vis a vis describing/enabling the prevention of migraine.

Claims 31 and 32 currently stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement and enablement requirement. In the Examiner's estimation, a claim for the prevention of migraine requires showings of specific dosages different from those described in the Specification as noted above along with evidence of non-toxicity at such doses, as well as a 100% cure rate. The Examiner is referred to the above arguments as they pertain directly to this second rejection based on section 112. Examiner is also directed to M.P.E.P. 2164.01(c), 2nd paragraph

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The asserted additional requirements for clinical data are simply not the law with regard to methods of treatment. Note that there is no claim limitation to the

exact dose to be used or that such dose be free of any associated toxicities. (Again, "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). It is in fact well known in the art how to determine if a patient is a candidate for preventative treatment for migraine. The National Migraine Association website states:

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> Prophylactic Treatment: Preventative medication may be prescribed for patients who have frequent headaches (3 or more a month) that do not respond to abortive treatment. Studies have shown that as many as 40% of these patients may benefit from preventative treatment.

It is well within the skill of the art to take the guidance given as referenced above to set appropriate dosing for any given clinical candidate selected among the compounds within the scope of the claims and for a physician to adjust such dosing as needed for a given patient under their care. Furthermore, it has never been a requirement that a pharmaceutical agent provide a 100% cure rate to be patentable. The rejection must be withdrawn.

8. Whether Claims 9 and 30 are unpatentable under 35 U.S.C. 112, first paragraph as being indefinite for failing to include quantitative limitations.

Claims 9 and 30 currently stand rejected under 35 U.S.C. 112, first paragraph as being indefinite. The Examiner asserts that the Claims are self conflicting because they are pharmaceutical composition claims but do not recite any quantitative limitations such as "an anti-migraine effective amount."

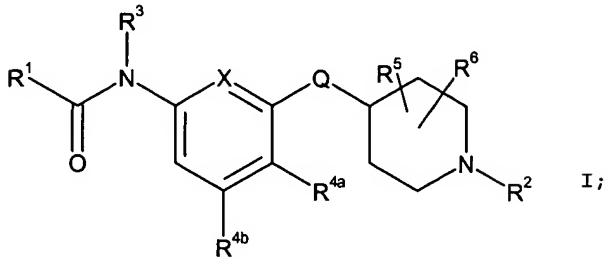
Examiner again places new and arbitrary requirements on Applicants. A

composition of matter claim is complete if it clearly states what the composition is comprised of. In the present Claims, the composition is defined as "comprising a compound according to Claim 1 (29) and a pharmaceutical carrier, diluent, or excipient. The ordinarily skilled person in the art would clearly understand that the composition has 1) a compound of formula 1 (29) and 2) a carrier, diluent, or excipient. This is definite on its face.

Examiner places an additional requirement that pharmaceutical composition, one has to include quantities so as to make the composition neither ineffective nor toxic. However, again, it is not necessary for Applicant to recite what quantities of the various components are to be in a composition of matter if such is not necessary to render the composition novel and non-obvious. It is not alleged that the composition is either anticipated or obvious based on quantities of the compound in the composition. Such a limitation is an unnecessary narrowing of the scope of the invention being claimed. The composition as claimed is in fact clearly bounded and unambiguous. The rejection must be withdrawn.

Claims Appendix

1. A compound of formula I:



I;

or a pharmaceutically acceptable acid addition salt thereof, where;

Q is oxygen or sulfur;

X is $-C(R^{4c})=$ or $-N=$;

R^1 is mono- di-, or tri-substituted phenyl wherein the substitutions are independently selected from halo, C_1-C_2 alkoxy, trifluoromethyl, trifluoromethoxy, and trifluoroethoxy;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

R^{4a} and R^{4b} are hydrogen;

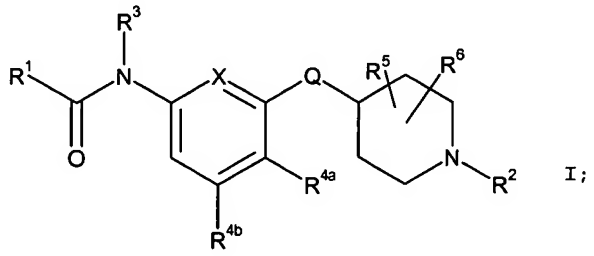
When X is $-C(R^{4c})=$, R^{4c} is hydrogen;

R^5 is hydrogen; and

R^6 is hydrogen.

9. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutical carrier, diluent, or excipient.

14. A method for the treatment or prevention of migraine in a mammal comprising administering to a mammal in need of such treatment or prevention an effective amount of a compound of formula I:



I;

or a pharmaceutically acceptable acid addition salt thereof, where;

Q is oxygen or sulfur;

X is $-C(R^{4c})=$ or $-N=$;

R^1 is mono- di-, or tri-substituted phenyl wherein the substitutions are independently selected from halo, C_1-C_2 alkoxy, trifluoromethyl, trifluoromethoxy, and trifluoroethoxy;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

R^{4a} and R^{4b} are hydrogen;

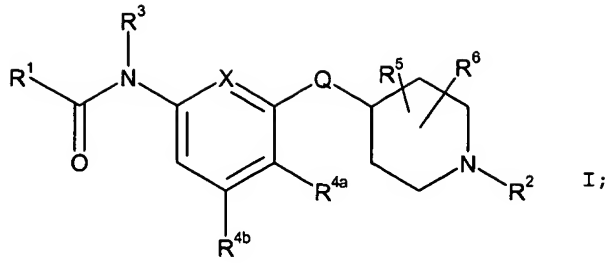
When X is $-C(R^{4c})=$, R^{4c} is hydrogen;

R^5 is hydrogen; and

R^6 is hydrogen.

15. The method according to Claim 14 wherein the mammal is a human.

29. A compound of formula I:



I;

or a pharmaceutically acceptable acid addition salt thereof, where;

Q is oxygen or sulfur;

X is –C(H)= or –N=;

R^1 is a substituted or unsubstituted heterocycle wherein the heterocycle is selected from the group consisting of pyridinyl and thiophenyl;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

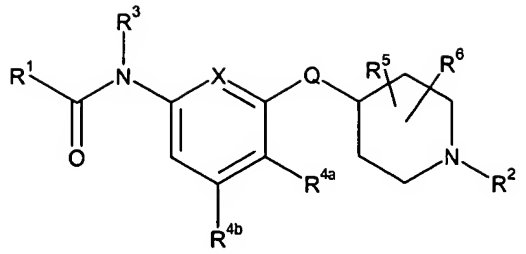
R^{4a} and R^{4b} are hydrogen;

R^5 is hydrogen; and

R^6 is hydrogen.

30. A pharmaceutical composition comprising a compound according to Claim 29 and a pharmaceutical carrier, diluent, or excipient.

31. A method for the treatment or prevention of migraine in a mammal comprising administering to a mammal in need of such treatment or prevention an effective amount of a compound of formula I:



I;

or a pharmaceutically acceptable acid addition salt thereof, where;

Q is oxygen or sulfur;

X is –C(H)= or –N=;

R^1 is a substituted or unsubstituted heterocycle wherein the heterocycle is selected from the group consisting of pyridinyl and thiophenyl;

R^2 is hydrogen or methyl;

R^3 is hydrogen;

R^{4a} and R^{4b} are hydrogen;

R^5 is hydrogen; and

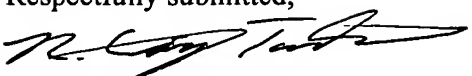
R^6 is hydrogen.

32. The method according to Claim 31 wherein the mammal is a human.

Evidence Appendix

(None)

Respectfully submitted,



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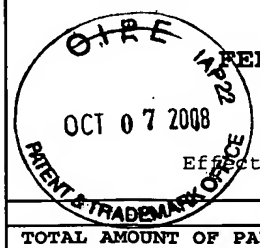
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

October 6, 2008

Please type a plus sign (+) inside this box → [+]



FEE TRANSMITTAL

Effective December 8, 2004

Complete if Known	
Serial No.	10/552131
Application Date	April 14, 2004
US Nat'l Entry Date (if applicable)	October 11, 2005
First Named Inventor	BLANCO-PILLADO Maria-Jesus
Group Art Unit	1625
Examiner Name	-
Conf. No.	7160
Attorney Docket Number	X14441

TOTAL AMOUNT OF PAYMENT	($) 970.00

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 05-0840

Deposit Account Name: Eli Lilly and Company

[X] Charge Any Additional Fee Required

[ ] Charge the Issue Fee Set in 37 CFR 1.18 at the time of allowance

FEE CALCULATION

1. **In connection with the filing, search and exam fees**

Code	Description	Fee	Fee Paid
1011	Basic filing fee (Utility)	$310.00	
1111	Utility search fee	$510.00	
1311	Utility examination fee	$210.00	

SUBTOTAL (1) ($)

Code	Total claims	Extra	Fee Paid ($)
1202	___ - 20 =	___ X 50 =	$

Independent claims

1201	___ - 3 =	___ X 210 =	$

1203	Multiple Dependent Claim	Yes or No	370 = (if yes)	$

Claims and Excess Length Fees

1081 Total length (spec + drawings)

____ - 100 = ____ excess pages

$_____

No extra charge for first 100 pages. Must pay $260 for each adtl 50 pages (or fraction thereof).

SUBTOTAL (2) ($) -0-

FEE CALCULATION (continued)

3. **ADDITIONAL FEES**

Large Entity Fee Code	Large Entity Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge-late filing fee or oath	
1052	50	Surcharge-late provisional filing fee or cover sheet.	
1053	130	Non-English specification	
1251	120	Extension for reply within first month	
1252	460	Extension for reply within second month	460
1253	1,050	Extension for reply within third month	
1254	1,640	Extension for reply within fourth month	
1255	2,230	Extension for reply within fifth month	
1401	510	Notice of Appeal	
1402	510	Filing a brief in support of an appeal	510
1452	510	Petition to revive-unavoidable	
1453	1,540	Petition to revive-unintentional	
1502	1,440	Utility issue fee (or reissue)	
122	130	Petitions to the Commissioner	
1801	810	Request for Continued Examination (RCE)	

Other fee (specify)

Other fee (specify)

Other fee (specify)

Other fee (specify)

SUBTOTAL (3) ($) 970

SUBMITTED BY

Complete (if applicable)

Typed or Printed Name	R. Craig Tucker	Reg. Number	45,165
Signature		Date	October 6, 2008